Background and aims

- Semaglutide is a glucagon-like peptide-1 analogue formulated both as an approved once-weekly subcutaneous (s.c.) injection and a once-daily oral tablet in development for the treatment of type 2 diabetes (T2D).[1,2]
- The s.c. and oral formulations have been studied across a series of clinical trials in the SUSTAIN and PIONEER programmes, respectively.[3–12]
- The long half-life and daily dosing with oral semaglutide mitigate variability in absorption, leading to stable steady-state exposure levels. Nevertheless, the plasma concentrations are more variable with oral compared with s.c. administration.[1]
- Using population data from the SUSTAIN and PIONEER trials, we analysed whether the route of administration affected the efficacy and gastrointestinal (GI) tolerability vs exposure for semaglutide.

Materials and methods

Population data

- Response data were compared from:
  - Four trials (SUSTAIN 1, 2, 3 and SUSTAIN-Japan) of once-weekly s.c. semaglutide 0.5 and 1.0 mg evaluated after 30 weeks.[3–6]
  - Six trials (PIONEER 1, 2, 3, 5, 8 and 9 [PIONEER 9 conducted in Japan]) of once-daily oral semaglutide 3, 7 or 14 mg given for 26 weeks.[7–12]

Population pharmacokinetic model

- A population pharmacokinetic (PK) model was developed for each PIONEER and SUSTAIN dataset.[13]

Exposure–response models for efficacy and tolerability

- For HbA_{1c} and body weight change from baseline, the data were adequately described by maximum response (E_{max}) models with baseline HbA_{1c}, sex and trial population as main influential factors, and additional effects of diabetes duration, race and ethnicity.
- For binary safety endpoints (proportions of patients with nausea and vomiting, respectively), linear models on the logit scale were used. The main influential factors were sex and trial population.

Propensity score matching

- Overall the PIONEER and SUSTAIN exposure–response populations were similar, with the main difference being the inclusion of a dedicated study of patients with moderate renal impairment and a trial with concomitant insulin treatment in the PIONEER programme.
- Propensity score matching was used to analyse the effect of balancing the differences between the SUSTAIN and PIONEER populations based on baseline HbA_{1c}, trial population, diabetes duration, race, ethnicity and sex (Figure 1).

Results

- Before matching, data from 1552 patients from SUSTAIN and 3003 patients from PIONEER were included. After matching, both datasets contained 1551 patients with well-matched characteristics, although the SUSTAIN population contained more Asian patients and more patients with mild renal impairment (Table 1).
- Population PK analysis indicated dose-proportional PK profiles for both oral and s.c. semaglutide, with body weight the main factor influencing exposure.
- The exposure range was wider with oral vs s.c. administration, but with considerable overlap between oral semaglutide 7 and 14 mg, and s.c. semaglutide 0.5 and 1.0 mg, indicating consistent exposure across formulations.
- Exposure–response analyses showed greater HbA_{1c} and body weight reductions, and more GI side effects, with increasing semaglutide exposure.
- Exposure–response relationships for efficacy and safety were consistent across the SUSTAIN and PIONEER datasets, and even more consistent with overlapping 95% confidence intervals when propensity matching was used (Figure 2 and key result panel).

Conclusions

Oral and s.c. semaglutide have **consistent efficacy and GI safety profiles** vs exposure

Propensity matching helped to confirm that **the differences between trial populations did not influence** the exposure–response evaluation

Increasing semaglutide exposure is associated with **greater efficacy** and **an increased proportion of patients reporting GI side effects**

These trials were sponsored by Novo Nordisk and are registered with ClinicalTrials.gov (NCT02054897 [SUSTAIN 1], NCT01930188 [SUSTAIN 2], NCT01885208 [SUSTAIN 3], NCT02254291 [SUSTAIN-Japan], NCT02906930 [PIONEER 1], NCT02863328 [PIONEER 2], NCT02607865 [PIONEER 3], NCT02827708 [PIONEER 5], NCT03021187 [PIONEER 8], NCT03018028 [PIONEER 9]).
The authors acknowledge the medical writing assistance of Stephen Purver of Spirit Medical Communications Group Ltd.
Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain, 16–20 September 2019.

https://qrs.ly/qjabn92

Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide

RV Overgaard (RUVO@novonordisk.com), A Navarria, CL Hertz, SH Ingwersen
Novo Nordisk A/S, Søborg, Denmark

Key results

Change from baseline in HbA_{1c} in the propensity score matched population.

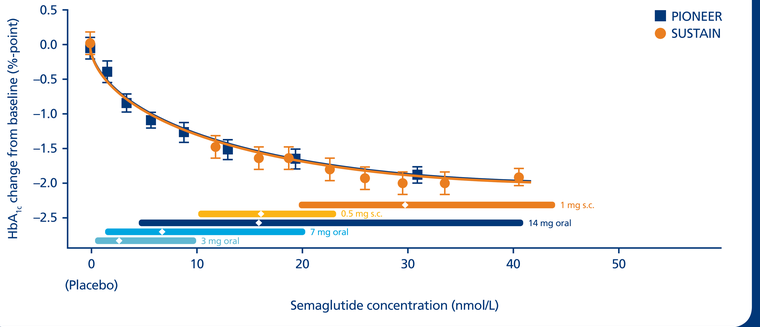


Figure 1 Propensity score matching – illustrative principle.

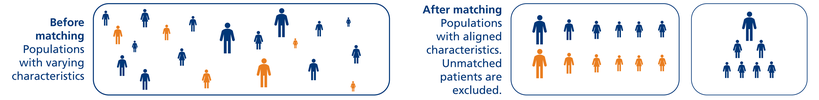
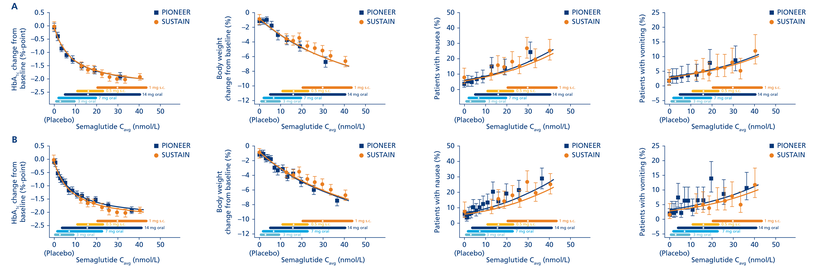


Figure 2 Efficacy and GI side effects by semaglutide exposure: **A**, propensity score matched populations; **B**, unmatched populations.



Data (circles and squares) are means and 95% CIs at week 26 for PIONEER and week 30 for SUSTAIN. Exposure is presented as ten quantiles of C_{avg} for semaglutide and one quantile for placebo (at C_{avg} of 0 nmol/L). The fitted solid line represents covariate-adjusted, model-derived relations for each programme. The horizontal lines along the x-axes represent medians and 90% exposure ranges with the median exposure represented by a diamond. Data from SUSTAIN 1, 2, 3, SUSTAIN-Japan and PIONEER 1, 2, 3, 5, 8 and 9. C_{avg}, median semaglutide concentration; CI, confidence interval; GI, gastrointestinal; HbA_{1c}, glycated haemoglobin; s.c., subcutaneous.

Table 1 Patient baseline characteristics.

Category		PIONEER		SUSTAIN (N=1551)
		Unmatched (N=3003)	Matched (N=1551)	
Age, years		59.4 (10.9)	57.3 (10.5)	56.0 (10.6)
Female		1345 (44.8)	653 (42.1)	658 (42.4)
Race				
White, other		2034 (67.7)	971 (62.6)	834 (53.8)
Asian		779 (25.9)	487 (31.4)	647 (41.7)
Black or African American		190 (6.3)	93 (6.0)	70 (4.5)
Renal function				
Normal		1809 (60.2)	1099 (70.9)	1024 (66.0)
Mild impairment		865 (28.8)	415 (26.8)	502 (32.4)
Moderate impairment		329 (11.0)	37 (2.4)	25 (1.6)
HbA_{1c}, %		8.1 ± 0.8	8.1 ± 0.9	8.1 ± 0.9
Body weight, kg		88.2 ± 21.9	87.2 ± 22.4	86.3 ± 22.7
Diabetes duration, years		9.5 ± 7.9	7.3 ± 6.3	7.2 ± 6.0
Background therapy				
1–2 OADs		1335 (44.5)	994 (64.1)	1077 (69.4)
Monotherapy		703 (23.4)	431 (27.8)	345 (22.2)
Insulin		845 (28.1)	12 (0.8)	–
Diet and exercise		120 (4.0)	114 (7.4)	129 (8.3)
Maintenance dose				
Placebo		572 (19.0)	191 (12.3)	129 (8.3)
0.5 mg s.c.		–	–	556 (35.8)
1.0 mg s.c.		–	–	866 (55.8)
3 mg oral		629 (20.9)	345 (22.2)	–
7 mg oral		620 (20.6)	331 (21.3)	–
14 mg oral		1182 (39.4)	684 (44.1)	–

Data are n (%) or mean ± SD. HbA_{1c}, glycated haemoglobin; OAD, oral antidiabetic drug; s.c., subcutaneous; SD, standard deviation.

References:

(**1**) Buckley et al. Sci Transl Med 2018;10:eaar7047;
(**2**) Aroda et al. Diabetes Metab 2019;pii: S1262–3636(18)30222–2;
(**3**) Seino et al. Diabetes Obes Metab 2018;20:378–388;
(**4**) Sorli et al. Lancet Diabetes Endocrinol 2017;5:251–260;
(**5**) Ahrén et al. Lancet Diabetes Endocrinol 2017;5:341–354;
(**6**) Ahmann et al. Diabetes Care 2018;41:258–266;
(**7**) Aroda et al. Diabetes Care 2019;pii: dc190749;
(**8**) Montanya et al. Diabetes 2019;68(suppl 1):54-OR;
(**9**) Rosenstock et al. JAMA 2019;321:1466–1480;
(**10**) Mosenzon et al. Lancet Diabetes Endocrinol 2019;7:515–527;
(**11**) Zinman et al. Diabetes 2019;68(suppl 1):985-P;
(**12**) Yamada et al. J Diabetes Investig 2019;10(suppl 1):All-6-11;
(**13**) Carlsson Petri et al. Diabetes Ther 2018;9:1533–1547.